REMARKS

Upon entry of the claim amendments submitted herewith, claims 14 and 15, claims 19-29, claim 42, and claims 44-53 are pending. Applicant has cancelled claim 43 without prejudice and reserves the right to prosecute the subject matter in a continuing application filed during the pendency of the instant application. Applicants have amended claims 15, 42, 44-47, 52 and 53 as indicated herein. The amendments to claims 15 and 42-47 find basis throughout the instant specification and particularly on page 8, line 6; page 9, line 2; and page 80, line 14. The amendments to claims 52 and 53 were made to correct antecedent basis.

No new matter has been introduced.

Allowable Subject Matter

Applicant thanks the Examiner for indicating the allowability of claims 14, 19-29 and 48-51.

Rejections under 35 U.S.C. §112

Claims 52 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that claim 52 is indefinite because the recited limitation "wherein each internucleoside linkage" in the first line of the claim lacks sufficient antecedent basis. Claim 52 is amended herein to recite "further comprising phosphorothioate linkages for each internucleoside linkage."

The Examiner states that claim 53 is indefinite because the recited limitation "wherein each cytosine" in the first line of the claim lacks sufficient antecedent basis. Claim 53 is amended herein to recite "further comprising a 5-methylcytosine for each cytosine."

Applicant believes that the amendments to claims 52 and 53 render the claims definite and the rejection therefore moot.

The Rejection of Claim 15 under 35 U.S.C. §102 or 35 U.S.C. § 103

In the Office Action mailed January 25, 2006, the Examiner indicated that claims 14 and 15 would be allowable if written in independent form including all of the limitations of the base claim and deleting non-elected subject matter. Claims 14 and 15 were amended in Applicant's

Amendment dated March 16, 2006 to incorporate the limitations of the base claim, claim 1, and to delete non-elected sequences from the claim.

In the instant Office Action, the Examiner has withdrawn the allowability of claim 15 in view of new art rejections. The Examiner has rejected claim 15 under 35 U.S.C. 102(b) or 35 U.S.C. 103(a) as being anticipated by or obvious over Bentwich *et al.* (U.S. 2006/0003322). The Examiner has also rejected claim 15 under 35 U.S.C. 102(e) or 35 U.S.C. 103(a) as being anticipated by or obvious over Zhou *et al.* (2005/0026164).

Applicant respectfully disagrees.

1) Rejection of Claim 15 Under 35 U.S.C. 102(b) or 35 U.S.C. 103(a) as being anticipated by or obvious over Bentwich *et al.* (U.S. 2006/0003322).

Propriety of Rejection under 35 U.S.C. 102(b)

Applicant believes a rejection under 35 U.S.C. 102(b) is improper. A 102(b) rejection can only be made when the publication is more than a year prior to the filing date of the instant application. MPEP § 2132.01 states "when the reference is a U.S. patent published within the year prior to the application filing date, a 35 U.S.C. 102(e) rejection should be made."

The Examiner's Rejection

The Examiner has rejected claim 15 using prior art which allegedly discloses and/or teaches an oligonucleotide 22 nucleobases in length, targeted to a nucleic acid encoding a human forkhead box O1A wherein the compound is 90.9% complementary to the nucleic acid encoding a human forkhead box O1A. The Examiner points specifically to the sequence alignment of SEQ ID NO. 155128 from Bentwich *et al.*, result 1995 in database rnpbn. The Examiner concludes that the nucleic acid sequence taught by Bentwich *et al.* meets the structural limitations of claim 15. The Examiner further states, citing MPEP 2112, that "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103." The examiner therefore reasons that the instant claims are anticipated by or, in the alternative, obvious over Bentwich *et al.*

The claims

Claim 15 is directed to a compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding forkhead box O1A, wherein the compound is at least 70% complementary to said nucleic acid molecule, wherein the compound inhibits the expression of said nucleic acid

molecule, and wherein the compound comprises at least 8 consecutive nucleobases of SEQ ID NO: 172.

The Disclosure in Bentwich *et al.* Does Not Anticipate Claim 15 Under 35 U.S.C. 102

The sequence alignment provided by the Examiner shows that the *complement* of SEQ ID 155128 shares 20 nucleobases in common with a 22 nucleobase region of a human forkhead box O1A encompassing nucleotides 2713 to 2734. The term complementary is defined herein as "the capacity for precise pairing between two nucleobases...if a nucleobase at a certain position of an oligonucleotide (an oligomeric compound), is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid...then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be a complementary position." (See, for example, the instant specification at page 7, lines 21-26). Thus SEQ ID NO 155128 is 90.9% complementary with this region of forkhead box O1A.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *See e.g., In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990). Bentwich *et al.* do not disclose all elements of claim 15. Claim 15 requires a single compound that 1) is both 70% complementary to forkhead box O1A and has 8 consecutive nucleobases of SEQ ID NO: 172; 2) is specifically targeted to a nucleic acid molecule encoding forkhead box O1A; and 3) inhibits the expression of forkhead box O1A. First, while the specific sequence in SEQ ID NO 155128 of Bentwich *et al.* is 90.9% complementary with a region of forkhead box O1A, the sequence does not comprise at least 8 consecutive nucleobases of instant SEQ ID NO 172. Additionally, the complement of SEQ ID NO 155128 is not at least 70% complementary to forkhead box O1A. Further, as amended, the claim is directed to an antisense oligonucleotide targeted to SEQ ID NO 4, a human genomic sequence of forkhead box O1A, making it clear that the oligonucleotide having at least 8 nucleobases of instant SEQ ID NO 172 is a single antisense sequence to forkhead box O1A and is 70% complementary to forkhead box O1A. No single sequence disclosed by Bentwich *et al.* that would be used as an antisense oligonucleotide targeted to forkhead box O1A has both limitations described above; namely, at least 70% complementarity to forkhead box O1A and at least 8 nucleobases in common with instant SEQ ID NO 172. Therefore, the sequence disclosed by Bentwich *et al.* does not meet these structural limitations of claim 15.

Second, Bentwich *et al.* do not disclose that the oligonucleotide in SEQ ID 155128 is targeted to a nucleic acid encoding a human forkhead box O1A or that it inhibits the expression of a nucleic acid encoding forkhead box O1A. The sequence in SEQ ID 155128 is disclosed only in the

sequence listing and nowhere else. Applicant was unable to find any additional disclosure regarding this sequence other than the sequence listing itself. In fact, it is unclear to Applicant whether this sequence is intended by Bentwich *et al.* to represent a GAM sequence capable of binding a target or the target sequence itself or some other sequence. The Examiner is reminded that it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *See e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.,* 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Without more, the Examiner has not provided a *prima facie* case of anticipation.

To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.*, 334 U.S.P.Q.2d 1565 (Fed. Cir. 1995). As addressed above, Bentwich *et al.* do not explicitly disclose any elements of claim 15. Additionally, the reference is silent with regard to any features that might be deemed inherent to the sequence listed in SEQ ID 155128. To serve as anticipation when a reference is silent about the alleged inherent characteristic, such gap in the reference may be filled by extrinsic evidence. *See e.g., Continental Can Co. USA Inc. v. Monsanto Co.*, 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991). The Examiner fails to provide any extrinsic evidence that makes clear that the missing descriptive matter is always present in the thing disclosed by Bentwich *et al*, and that it would be so recognized by persons of ordinary skill in the art; namely, that SEQ ID NO 155128 is targeted to a nucleic acid encoding forkhead box O1A and inhibits the expression of forkhead box O1A. The Examiner provides only a sequence alignment which shows the complement of SEQ ID 155128 sharing 20 nucleobases in common with a 22 nucleobase region of a human forkhead box O1A encompassing nucleotides 2713 to 2734 with no discussion of the results of such sequence alignment. Nor does the Examiner point to any disclosure within the application disclosing that SEQ ID NO 155128 is specifically targeted to a nucleic acid encoding forkhead box O1A or that it inhibits the expression of forkhead box O1A. Thus, the Examiner has failed to establish a *prima facie* case that the Bentwich *et al.* reference anticipates claim 15.

The Teachings in Bentwich *et al.* Do Not Render Claim 15 Obvious Under 35 U.S.C. 103

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103, the combination of the cited references must actually teach or suggest the claimed invention. Importantly, all claim limitations must be taught or suggested by the prior art to establish that claims are *prima facie* obvious. *See, e.g.,* MPEP 2143.03 and *In re Lowry*, 32 F.3d 1579, 32 U.S.P.Q.2d

1031 (Fed. Cir. 1994), citing *In re Gulack*, 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983), citing *In re Royka*, 490 F.2d 981, 180 U.S.P.Q.2d 580 (CCPA 1974).

As presented above, Bentwich *et al.* do not teach or suggest the steps of claim 15, including 1) a sequence targeted to a nucleic acid molecule encoding forkhead box O1A; 2) a sequence that is both 70% complementary to forkhead box O1A and which has 8 consecutive nucleobases of SEQ ID NO: 172; and 3) a sequence that inhibits the expression of forkhead box O1A. Specifically, the sequence in SEQ ID NO 155128 does not comprise at least 8 consecutive nucleobases of instant SEQ ID NO 172. Additionally, the complement of SEQ ID NO 155128 is not at least 70% complementary to forkhead box O1A. Further, as amended herein, the claim is now directed to an antisense oligonucleotide targeted to SEQ ID NO 4, a human genomic sequence of forkhead box O1A, making it clear that the oligonucleotide having at least 8 nucleobases of instant SEQ ID NO 172 is an antisense sequence to forkhead box O1A and is 70% complementary to forkhead box O1A. No single sequence disclosed by Bentwich *et al.* that would be used as an antisense oligonucleotide targeted to forkhead box O1A has both limitations described above; namely, at least 70% complementarity to forkhead box O1A and at least 8 nucleobases in common with instant SEQ ID NO 172. Therefore, the sequence disclosed by Bentwich *et al.* does not meet these structural limitations of claim 15.

Further, Bentwich *et al.* do not teach that the oligonucleotide in SEQ ID 155128 is targeted to a nucleic acid encoding a human forkhead box O1A. Further, Bentwich *et al.* do not teach or suggest that the sequence in SEQ ID 155128 inhibits the expression of a nucleic acid encoding forkhead box O1A. As stated above, the sequence in SEQ ID 155128 is disclosed only in the sequence listing and nowhere else. Applicant was unable to find any additional teaching regarding this sequence or forkhead box O1A generally. Without more, the Examiner has not provided a *prima facie* case of obviousness because the Examiner has not identified wherein the reference teaches anything about the sequence. To find a sequence that happens to be complementary to the instant target and proclaim that it posses the properties of the invention when the prior art reference does not teach or suggest any such properties, amounts to improper hindsight reconstruction wherein that which only the inventor taught is used against its teacher. *See e.g., W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983).

In addition, Bentwich *et al.* is nonanalogous Art. Two criteria have evolved for determining whether prior art is analogous: 1) whether the art is from the same field of endeavor, regardless of the problem addressed, and 2) if the reference is not within the field of the inventor's endeavor,

whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved. *See e.g., In re Clay,* 966 F.2d 656, 23 USPQ2d 1058 (Fed. Cir. 1992). Bentwich *et al.* is not within the same field of endeavor. The reference is directed to the bioinformatic detection of a group of regulatory genes (GAM genes) and possible use of these genes. Thus, the field of endeavor for this reference is bioinformatics and its use in gene detection and functional identification. The instant application is specifically directed to the modulation of forkhead box O1A expression. There is no mention of forkhead box O1A in the reference. One of ordinary skill in the art would not look to, nor would ever find by searching strategies applied in the art, this published application for teachings that would be applicable in the design of modulators of forkhead box O1A. The GAM sequences together with alleged target sequences make up the 1,388,402 sequences in the sequence listing filed by Bentwich et al. The published application discloses only four (4) GAM genes and related target sequences. None of these sequences are SEQ ID NO 155128. Without more, one skilled in the relevant art would not find this reference by searching strategies applied in the art. If by some chance one of skill in the art did happen upon this reference, one would not do what the examiner has done and sift through the 1,388,402 sequences provided by Bentwich et al. to find the one sequence disclosed in SEQ ID 155128 that happens to be complementary to a nucleic acid encoding forkhead box O1A. The Examiner's ability to find this reference results only from knowledge of the sequence provided in the instant application and the sequence searching strategies employed by the PTO.

Further, the reference is not reasonably pertinent to the problem with which the instant application is involved. The instant application is directed to the design of antisense to forkhead box O1A. Bentwich *et al.* teach that one possible use of the GAM genes is the inhibition of a target gene. However, the only means of inhibition suggested is utilizing a DNA vector and an RNAi pathway (see e.g., claims 11-12). There is no mention of the design of antisense compounds in the reference or of forkhead box O1A. Therefore, one of ordinary skill in the art would not look to this published application for teachings that would be applicable to the specific problem of designing antisense oligonucleotides to forkhead box O1A.

Not only is there no motivation to chose Bentwich *et al.* to solve the instant problem, if one of skill in the art were to choose Bentwich, *et al.*, the instant result could not have been achieved. Bentwich *et al.* teach that the specific inhibitor site (active site) to which the RNA transcripts of the invention hybridize and inhibit expression is located in the 3'untranslated region of the target genes.

This teaches away from instant SEQ ID 172 which is complementary to a region (nucleotides 2286-2305) of forkhead box O1A outside the 3' untranslated region.

2) Rejection of Claim 15 Under 35 U.S.C. 102(e) or 35 U.S.C. 103(a) as being anticipated by or obvious over Zhou *et al.* (U.S. 2005/0026164)

The Examiner's Rejection

The Examiner has rejected claim 15 using prior art which allegedly discloses and/or teaches an oligonucleotide 15 nucleobases in length, targeted to a nucleic acid encoding a human forkhead box O1A wherein the compound is 100% complementary to the nucleic acid encoding a human forkhead box O1A. The Examiner points specifically to the sequence alignment of SEQ ID NO. 643422 from Zhou *et al.*, result 27 in database rnpbn. The Examiner concludes that the nucleic acid sequence taught by Zhou *et al.* meets the structural limitations of claim 15. The Examiner further states, citing MPEP 2112, that "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103." The examiner therefore reasons that the instant claims are anticipated by or, in the alternative, obvious over Zhou *et al.*

Applicant respectfully disagrees.

Claim 15 is not Anticipated or Rendered Obvious by Zhou *et al.* Under 35 U.S.C. 102(e) or 35 U.S.C. 103(a)

First, the sequence of SEQ ID NO. 643422 is 25 nucleotides in length, not 15 as stated by the Examiner (See Examiner's own statement in the rejection of claims 42-47 on page 7 of the Office Action). Zhou *et al.* do not disclose, teach or suggest that the sequence may be used in truncated form. As such, the sequence as a whole has 7 mismatches with the human forkhead box O1A encoded by SEQ ID NO. 4 resulting in 72% complementarity. In an effort to advance prosecution, claim 15 is amended herein to recite an antisense oligonucleotide 8 to 80 nucleobases in length targeted to the nucleic acid molecule of SEQ ID NO: 4 encoding forkhead box O1A, wherein the compound is at least 75% complementary to said nucleic acid molecule, wherein the compound inhibits the expression of said nucleic acid molecule, and wherein the compound comprises at least 8 consecutive nucleobases of SEQ ID NO: 172. In light of the amendments set forth, Zhou *et al.* do not disclose, teach or suggest all of the limitations of claim 15. Specifically, SEQ ID NO 643422 disclosed by Zhou *et al.* is not at least 75% complementary to the nucleic acid molecule of instant

SEQ ID NO 4 encoding forkhead box O1A. Therefore, Applicant respectfully submits that the rejection is moot.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claim 42-47 under 35 U.S.C. 102(b) as being anticipated by Bentwich *et al.* (U.S. 2006/0003322). The Examiner has also rejected claim 15 under 35 U.S.C. 102(e) as being anticipated by Zhou *et al.* (2005/0026164).

Applicant respectfully disagrees.

1) Rejection of Claims 42-47 Under 35 U.S.C. 102(b) as being anticipated by Bentwich *et al.*

Propriety of Rejection under 35 U.S.C. 102(b)

As argued above, Applicant believes a rejection under 35 U.S.C. 102(b) is improper. See argument on page 6 of the instant Amendment.

Content of the Examiner's Rejection

The Examiner has rejected claims 42-47 using prior art which allegedly 'teaches' a compound 22 nucleotides in length comprising 20 nucleotides of SEQ ID NO. 172 wherein the compound is 90.9% complementary to a nucleic acid molecule encoding forkhead box O1A. The Examiner points specifically to the sequence alignment of SEQ ID NO. 155128. The Examiner concludes that Bentwich *et al.* anticipates claims 42-47.

The claims

Claims 42-47 are directed to a compound 15 to 30 nucleobases in length comprising at least 8 consecutive nucleobases of SEQ ID NO. 172 wherein the compound is at least 70%, 80%, 90% or 95% complementary to a nucleic acid molecule encoding forkhead box O1A.

The Disclosure in Bentwich *et al.* Does Not Anticipate Claims 42-47 Under 35 U.S.C. 102

Bentwich *et al.* disclose in SEQ ID NO. 155128 an oligonucleotide 22 nucleobases in length. The sequence alignment shows that the complement of SEQ ID 155128 shares 20 nucleobases in common with a 22 nucleobase region of a human forkhead box O1A encompassing nucleotides 2713 to 27348. Thus SEQ ID NO 155128 is 90.9% complementary with this region.

Anticipation requires the *disclosure* in a single prior art reference of each element of the claim under consideration. *See e.g., In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990). Bentwich *et al.* do not disclose all elements of claims 42-47. The Examiner points only to SEQ ID NO 155128. As argued above, the sequence in SEQ ID NO 155128, which is 90.9% complementary to a site on a

forkhead box O1A encompassing nucleotides 2713 to 2734, does not comprise at least 8 consecutive nucleobases of instant SEQ ID NO 172.

In addition, claim 42 is amended herein to recite an antisense oligonucleotide comprising at least 8 consecutive nucleobases of SEQ ID NO: 172 and which is at least 75% complementary to the nucleic acid molecule of SEQ ID NO 4 encoding forkhead box O1A. The complement of SEQ ID NO 155128 is not at least 75% complementary to forkhead box O1A. As discussed above, complementarity is defined herein as "the capacity for precise pairing between two nucleobases...if a nucleobase at a certain position of an oligonucleotide (an oligomeric compound), is capable of hydrogen bonding with a nucleobase at a certain position of a target nucleic acid...then the position of hydrogen bonding between the oligonucleotide and the target nucleic acid is considered to be a complementary position." (See, for example, the instant specification at page 7, lines 21-26). No single sequence disclosed by Bentwich *et al.* that would be used as an antisense oligonucleotide targeted to forkhead box O1A has both limitations described above; namely, at least 75% complementarity to forkhead box O1A and at least 8 nucleobases in common with instant SEQ ID NO 172.

Therefore, in light of the amendments put forth, the sequence disclosed by Bentwich *et al.* does not meet the structural limitations of claims 42-47 and Applicant respectfully submits that the rejection is rendered moot.

2) Rejection of Claims 42-47 Under 35 U.S.C. 102(e) as being anticipated by Zhou *et al.*

The Examiner's Rejection

The Examiner has rejected claims 42-47 using prior art which allegedly 'teaches' a compound 25 nucleotides in length comprising 15 nucleotides of SEQ ID NO. 172 wherein the compound is 100% complementary to a nucleic acid molecule encoding forkhead box O1A. The Examiner points specifically to the sequence alignment of SEQ ID NO. 643422. The Examiner concludes that Zhou *et al.* anticipates claims 42-47.

Claims

See description of claims supra.

The Disclosure in Zhou *et al.* Does Not Anticipate Claims 42-47 Under 35 U.S.C. 102

As indicated above, anticipation requires the *disclosure* in a single prior art reference of each element of the claim under consideration. Zhou *et al.* do not disclose all elements of claims 42-47 especially in light of the claim amendments provided herein.

Claim 42 is amended herein to recited that the compound comprises at least 8 consecutive nucleobases of SEQ ID NO: 172 and is at least 75% complementary to the nucleic acid molecule of SEQ ID NO 4 encoding forkhead box O1A. As indicated above in Applicants arguments regarding the rejection of claim 15, SEQ ID NO 643422 disclosed by Zhou *et al.* is not at least 75% complementary to the nucleic acid molecule of instant SEQ ID NO 4 encoding forkhead box O1A. Therefore, the rejection is moot.

In light of the amendments and remarks provided herein, Applicant believes that the Examiner's rejections have been fully addressed and rendered moot. Therefore, Applicant respectfully requests allowance of the pending claims.

Respectfully submitted,

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